General

Guideline Title

American Society of Clinical Oncology clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer.

Bibliographic Source(s)

Van Poznak CH, Temin S, Yee GC, Janjan NA, Barlow WE, Biermann JS, Bosserman LD, Geoghegan C, Hillner BE, Theriault RL, Zuckerman DS, Von Roenn JH. American Society of Clinical Oncology clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2011. 17 p. [77 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Hillner BE, Ingle JN, Chlebowski RT, Gralow J, Yee GC, Janjan NA, Cauley JA, Blumenstein BA, Albain KS, Lipton A, Brown S. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003 Nov 1;21(21):4042-57.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- March 22, 2016 – Opioid pain medicines : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC) and the American Society of Clinical Oncology (ASCO): In planning the 2011 update, ASCO changed the scope of the guidelines to reflect changes in the field since the previous guideline. Reflecting the Update Committee's

anticipation that data on new types of agents, including osteoclast inhibitors, may be available for future updates of this guideline, this guideline uses the term bone-modifying agents. The terminology in Recommendations 1, 2, 4, 6, and 7 has been changed from bisphosphonate to bone-modifying agent. The recommendations within the guideline focus on the drugs denosumab, zoledronic acid, and pamidronate because they are currently available in the United States.

Six of the recommendations are substantively the same as in the 2003 guidelines for bone-modifying agents for metastatic breast cancer. The current guideline has added a new recommendation regarding osteonecrosis of the jaw (ONJ), a condition recognized after the preparation of the 2003 guidelines. This guideline on metastatic breast cancer also reviews data on a new bone-modifying agent, denosumab. In contrast with the previous version, this guideline now focuses solely on patients with evidence of bone metastases. (See Table 1, "Summary of the 2011 Recommendations" in the original guideline document for more detailed information.)

Clinical Question 1

What are the indications for using bone-modifying agents to reduce the risk of skeletal-related events (SREs) in patients with metastatic breast cancer? When is the best time to initiate treatment with bone-modifying agents?

Recommendation 1. For patients with breast cancer who have evidence of bone metastases, denosumab 120 mg subcutaneously every 4 weeks, intravenous (IV) pamidronate 90 mg delivered over no less than 2 hours, or zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks is recommended. Starting bone-modifying agents in women with an abnormal bone scan and an abnormal computed tomography scan or magnetic resonance imaging showing bone destruction, but normal plain radiographs, is considered reasonable by Panel consensus based on the findings in women with lytic or mixed lytic/blastic changes on plain radiographs. Starting bone-modifying agents in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, computed tomography scans, or magnetic resonance imaging is not recommended outside of a clinical trial. There is insufficient evidence relating to efficacy to support one bone-modifying agent over another.

Clinical Question 2

What is the role of bone-modifying agents in the presence of extraskeletal metastases without evidence of bone metastases?

Recommendation 2. Starting bone-modifying agents in women without evidence of bone metastases even in the presence of other extraskeletal metastases is not recommended. This clinical situation has been inadequately studied using IV bisphosphonates or other bone-modifying agents and should be the focus of new clinical trials.

Clinical Question 3A

What are the renal safety concerns of bone-modifying agent therapy?

Recommendation 3A. In patients with a calculated serum creatinine clearance of more than 60 mL/min, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid administration is required. Use of bone-modifying agents among patients with reduced renal function has been incompletely assessed. The packet insert of zoledronic acid provides guidance for dosing when baseline serum creatinine clearance is ≥30 and less than 60 mL/min. Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided. The Panel recommends that serum creatinine be monitored before each dose of pamidronate or zoledronic acid, in accordance with U.S. Food and Drug Administration (FDA)-approved labeling. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly. The risk of hypocalcemia with denosumab dosed at 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance less than 30 mL/min or receiving dialysis. Monitor for hypocalcemia in patients with impaired creatinine clearance. There is no evidence to guide the interval for monitoring serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin in patients on denosumab, pamidronate, or zoledronic acid.

Clinical Question 3B

What are the osteonecrosis of the jaw (ONJ) safety concerns of bone-modifying agent therapy?

Recommendation 3B. ONJ is an uncommon but potentially serious condition associated with the use of bone-modifying agents. The Update Committee concurs with the revised FDA label for zoledronic acid and pamidronate and the FDA label for denosumab and recommends that all patients with cancer receive a dental examination and necessary preventive dentistry prior to initiating therapy with inhibitors of osteoclast function unless there are mitigating factors that preclude the dental assessment. These recommendations should be observed whenever possible. While receiving inhibitors of osteoclast function, patients should maintain optimal oral hygiene and, if possible, avoid invasive dental procedures that involve manipulation of the jaw bone or periosteum. Although most cases of ONJ have occurred in patients treated with IV bisphosphonates and bone-modifying agents who underwent an invasive dental procedure, cases have occurred spontaneously and have been reported in patients treated with other bone-modifying agents, including oral bisphosphonates and direct osteoclast inhibitors.

Clinical Question 4

What is the optimal duration of bone-modifying agent therapy for patients with metastatic breast cancer?

Recommendation 4. The Panel suggests that, once initiated, bone-modifying agents should be continued until evidence of substantial decline in a patient's general performance status. The Panel stresses that clinical judgment must guide what constitutes a substantial decline. There is no evidence addressing the consequences of stopping bone-modifying agents after one or more adverse SREs.

Clinical Question 5

What are the best intervals between dosing?

Recommendation 5. For patients with breast cancer who have evidence of bone destruction on plain radiographs, denosumab 120 mg subcutaneously every 4 weeks, IV pamidronate 90 mg delivered over 2 hours, or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended.

Clinical Question 6

What is the role of bone-modifying agents in control of pain secondary to bone metastases?

Recommendation 6. The Panel recommends that the current standards of care for cancer bone pain management be applied at the onset of pain, in concert with the initiation of bone-modifying agent therapy. This is required by good clinical practice. The standard of care for pain management includes the use of nonsteroidal anti-inflammatory agents, opioid and nonopioid analgesics, corticosteroids, adjuvant agents, interventional procedures, systemic radiopharmaceuticals, local radiation therapy, and surgery. Bone-modifying agents are an adjunctive therapy for cancer-related bone pain control and are not recommended as first-line treatment for cancer-related pain. IV pamidronate or zoledronic acid may be of benefit for patients with pain caused by bone metastases and contribute to pain relief when used concurrently with analgesic therapy, systemic chemotherapy, radiation therapy, and/or hormonal therapy. Bone-modifying agents have been associated with a modest pain control benefit in controlled trials.

Clinical Question 7

What is the role of biochemical markers of bone turnover to guide initiation of therapy in patients without a prior skeletal event, predict treatment response, guide adjustments to bone-modifying agent therapy, or independently predict future fractures?

Recommendation 7. The use of the biochemical markers to monitor bone-modifying agent use is not recommended for routine care.

Special Commentary on the Role of Vitamin D Deficiency and Bone-Modifying Agents

In the absence of definitive data, it is the Update Committee’s expert consensus that if there are no contraindications to calcium and vitamin D supplementation, then patients receiving bone-modifying agents should receive them at doses and schedules similar to those used in the clinical trials of the bone-modifying agents, both to support bone health and decrease the risk of bisphosphonate-induced hypocalcemia. U.S. health authorities generally recommend a minimum consumption of vitamin D of 200 U (5 µg) a day. For the prevention and treatment of osteoporosis in adults, vitamin D 800 U daily is often recommended.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Metastatic breast cancer with bone metastases

Guideline Category

Assessment of Therapeutic Effectiveness

Prevention

Treatment

Clinical Specialty

Internal Medicine

Oncology

Radiology

Surgery

Intended Users

Physicians

Guideline Objective(s)

To update the recommendations on the role of bone-modifying agents* in the prevention and treatment of skeletal-related events (SREs) for patients with metastatic breast cancer with bone metastases

*Reflecting the Update Committee's anticipation that data on new types of agents, including osteoclast inhibitors, may be available for future updates of this guideline, this guideline uses the term bone-modifying agents.

Target Population

Patients with breast cancer with evidence of bone metastases

Interventions and Practices Considered

1. Bone-modifying agents approved for breast cancer metastatic to the bone:
    - Denosumab
    - Pamidronate
    - Zoledronic acid
2. Close monitoring for hypocalcemia in patients with creatinine clearance <30 mL/min or on dialysis who may be treated with denosumab
3. Dental examination and preventive dentistry before using bone-modifying agents (BMAs)
4. Cancer bone pain management including standard of care and use of bone-modifying agents

Note: The use of the biochemical markers to monitor bone-modifying agent use was considered but not recommended for routine care.

Major Outcomes Considered

- Skeletal-related events (SREs)
- Time to SRE
- Pain
- Adverse events

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

For this guideline, computerized literature searches of MEDLINE and the Cochrane Collaboration Library were conducted. Searches of the English-language literature from January 2003 to July 15, 2009, were conducted to address each of the original guideline questions; additional searches on biochemical markers of bone turnover (August 28, 2009) and on osteonecrosis of the jaw (ONJ) (March 16, 2010) were conducted. A supplemental search limited to randomized controlled trials (RCTs) on efficacy and case-control or cohort studies on adverse events was conducted on November 11, 2010. Search terms included the following: "breast neoplasms," "metastasis," "bone density conservation agents," "diphosphonates," and "biologic markers." Additional terms included generic and brand names of bone-modifying agents. Searches for efficacy outcomes were limited to published phase III RCTs, systematic reviews, and meta-analyses. For adverse events, the search was broadened to include observational studies because some adverse events of bone-modifying agents are rare. The Update Committee recognized these data as not as significant as data from comparative studies. For biomarker studies, reports were examined of prospective studies or retrospective analyses of prospectively collected samples with prospective aspects. The literature search terms are available in Data Supplement 4. A summary of the literature search results is provided in a QUORUM diagram in Data Supplement 5. Update Committee members provided additional references from personal files. (See the "Availability of Companion Documents" field for data supplements.)

Inclusion and Exclusion Criteria

Articles were selected for inclusion if they met the following criteria: participants had metastatic breast cancer and participants were randomly assigned to receive a bone-modifying agent or placebo or an alternative intervention. Outcome measures for efficacy and adverse event studies included at least one of the following: skeletal-related events (SREs) and time to SRE, adverse events, pain, and quality of life (see Definition of Terms in the original guideline document).

Number of Source Documents

A total of 54 articles were included for data extraction

- 3 systematic reviews
- 14 randomized controlled trials (RCTs)
- 9 pooled/subset/secondary analyses of RCTs
- 26 cohort/case-control studies
- 1 other

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction

Relevant articles were selected and reviewed, and one reviewer extracted the data. For each article meeting the inclusion criteria, data were extracted on patient characteristics, study design and quality, intervention, and outcomes. The primary articles and the extracted data were available to the Update Committee and were discussed during the teleconferences.

Study Quality and Limitations of the Literature

The definition of skeletal-relating event (SRE) was not uniform across all studies; for example, some studies excluded hypercalcemia of malignancy (HCM). In addition, different efficacy end points were used in different trials. There is a low incidence of some adverse events.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The American Society of Clinical Oncology (ASCO) convened the Update Committee to lead the 2011 update. The Update Committee met, via three teleconferences, on February 1, February 22, and November 23, 2010, to consider the evidence for each of the 2011 recommendations. A writing group of the Update Committee and ASCO staff drafted the guideline. The guideline was circulated in draft form to the Update Committee.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The guideline developers reviewed published cost analyses.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

As per standard American Society of Clinical Oncology (ASCO) practice, the guideline was submitted to *Journal of Clinical Oncology* for peer review. The entire Update Committee, ASCO's Clinical Practice Guidelines Committee, and the ASCO Board of Directors reviewed and approved the final document.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The recommendations are based on published randomized controlled trials, systematic reviews, and cohort/case-control studies. Refer to the "Literature review and analysis" sections of the original guideline document for specific evidence for each recommendation.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate use of bone-modifying agents in metastatic breast cancer
- Intravenous (IV) pamidronate or zoledronic acid may be of benefit among women with pain caused by bone metastases to relieve pain when used concurrently with systemic chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.

Potential Harms

- Pamidronate and zoledronic acid are associated with renal deterioration, particularly in patients with pre-existing renal impairment and in patients who receive multiple cycles of bisphosphonate therapy. The incidence of renal deterioration associated with pamidronate (90 mg) or zoledronic acid (4 mg) ranged between 6.2% and 12%. New dosing guidelines for patients with pre-existing renal impairment were added to the zoledronic acid package insert in January 2005. These guidelines recommend a lower initial zoledronic acid dose (ranging from 3.0 to 3.5 mg) depending on the estimated creatinine clearance. No similar dosing guideline exists for pamidronate. Pamidronate and zoledronic acid should be withheld from patients developing renal deterioration. Once serum creatinine returns to within 10% of baseline, therapy can be resumed.
- Denosumab has been associated with statistically significantly less renal deterioration than zoledronic acid. In a study of denosumab versus zoledronic acid, renal toxicity occurred more frequently with zoledronic acid than denosumab. The denosumab packet insert states that patients with a creatinine clearance less than 30 mL/min or receiving dialysis are at a greater risk of severe hypocalcemia than patients with normal renal function. The Update Committee recommends monitoring of electrolytes and renal function on a regular basis during therapy with bone-modifying agents.
- Longer follow-up from the zoledronic acid versus pamidronate studies has not changed the 2003 guideline's conclusion that the safety of the two agents seems to be similar with respect to nonrenal adverse events. The new agent, denosumab, demonstrated similar rates of nausea and vomiting compared with bisphosphonates and lower rates of arthralgia and asthenia. Acute-phase reactions were reported with both bisphosphonates and denosumab, although at lower rates with the latter. No new reports of ocular adverse effects were identified within the parameters of this guideline's literature search.
- Osteonecrosis of the jaw (ONJ) has been seen in patients treated with denosumab. The population incidence/prevalence and the etiology of ONJ remain unknown. The FDA labeling of denosumab, pamidronate, and zoledronic acid advises that patients should maintain good oral hygiene and have preventive dental examinations before initiating therapy, as well as avoid invasive dental procedures whenever possible. If an invasive manipulation of the bone underlying the teeth is clinically indicated before starting bone-modifying agent therapy, initiation of bone-modifying agent therapy should be ideally delayed for 14 to 21 days to allow for wound healing, if the clinical situation permits. The incidence of ONJ specifically in women with breast cancer metastatic to the bone seems to range from approximately 2.5% to 8.8% in cohort studies.

Qualifying Statements

Qualifying Statements

The American Society of Clinical Oncology's (ASCO's) practice guidelines reflect expert consensus based on clinical evidence and literature available at the time they are written and are intended to assist physicians in clinical decision making and identify questions and settings for further research. Because of the rapid flow of scientific information in oncology, new evidence may have emerged since the time a guideline was submitted for publication. Guidelines are not continually updated and may not reflect the most recent evidence. Guidelines address only the topics specifically identified in the guideline and are not applicable to interventions, diseases, or stages of disease not specifically identified. Guidelines cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge of the patient, to determine

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Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Van Poznak CH, Temin S, Yee GC, Janjan NA, Barlow WE, Biermann JS, Bosserman LD, Geoghegan C, Hillner BE, Theriault RL, Zuckerman DS, Von Roenn JH. American Society of Clinical Oncology clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2011. 17 p. [77 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2000 Mar (revised 2011)

Guideline Developer(s)

American Society of Clinical Oncology - Medical Specialty Society

Source(s) of Funding

American Society of Clinical Oncology (ASCO)

Guideline Committee

Update Committee

Composition of Group That Authored the Guideline

Panel Members: Catherine H. Van Poznak, Sarah Temin, Gary C. Yee, Nora A. Janjan, William E. Barlow, J. Sybil Biermann, Linda D. Bosserman, Cindy Geoghegan, Bruce E. Hillner, Richard L. Theriault, Dan S. Zuckerman, and Jamie H. Von Roenn

Financial Disclosures/Conflicts of Interest

The Update Committee was assembled in accordance with American Society of Clinical Oncology (ASCO)'s Conflict of Interest Management Procedures for Clinical Practice Guidelines ("Procedures," summarized at www.asco.org/guidelinescoi). Members of the Update Committee completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Committee did not disclose any of these relationships.

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership: None; Consultant or Advisory: Linda Bosserman, Amgen (C), Roche (C); Catherine Van Poznak, Amgen (C); Gary Yee, Amgen (C), Roche (C); Stock Ownership: None; Honoraria: Linda Bosserman, Abraxis BioScience, Amgen, Roche; Research Funding: Catherine Van Poznak, Amgen, Novartis; Expert Testimony: None; Other Remuneration: None

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Hillner BE, Ingle JN, Chlebowski RT, Gralow J, Yee GC, Janjan NA, Cauley JA, Blumenstein BA, Albain KS, Lipton A, Brown S. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003 Nov 1;21(21):4042-57.

Guideline Availability

Electronic copies: Available from the American Society of Clinical Oncology (ASCO) Web site.

Print copies: Available from Clinical Oncology, Cancer Policy and Clinical Affairs, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; E-mail: guidelines@asco.org.

Availability of Companion Documents

The following are available:

- American Society of Clinical Oncology (ASCO) clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. Executive summary. 2011. 9 p. Electronic copies: Available in Portable Document Format (PDF) from the American Society of Clinical Oncology (ASCO) Web site.
- American Society of Clinical Oncology (ASCO) clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. Slide set. 2011. 29 p. Electronic copies: Available in Portable Document Format (PDF) and PowerPoint from the ASCO Web site.
- Metastatic breast cancer bone modifying agents guideline update. Data supplements. 2011. 17 p. Electronic copies: Available in Portable Document Format (PDF) from the ASCO Web site.

Patient Resources

The following is available:

- What to Know: ASCO's guideline on bone-modifying drugs for breast cancer. Alexandria (VA): American Society of Clinical Oncology; 2011 Feb. Electronic copies: Available from the American Society of Clinical Oncology Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC Summary was completed by ECRI on September 21, 2000. The guideline developer was provided with a copy of this NGC summary for review, but to date, NGC has not received any comments from the guideline developer. This guideline was updated by ECRI on February 16, 2004. The updated information was verified by the guideline developer on February 26, 2004. This summary was updated by ECRI on March 28, 2005, following the U.S. Food and Drug Administration advisory on Zometa (zoledronic acid). This summary was updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on May 20, 2005, following the U.S. Food and Drug Administration advisory on Aredia (pamidronate disodium) and Zometa (zoledronic acid). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI Institute on June 15, 2011. This summary was updated by ECRI Institute on September 18, 2015 following the U.S. Food and Drug Administration advisory on non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI Institute on June 2, 2016 following the U.S. Food and Drug Administration advisory on Opioid pain medicines.

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